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13. ABSTRACT ***(Maximum 200 Words)***

We propose to study 10 healthy postmenopausal women who normally exercise. We will ask these women to have their blood drawn before and after an hour of exercise outdoors on a sunny day and then a week later indoors on a treadmill in a room with only indoor lighting. We propose that exercise done outdoors will have a different effect on vascular endothelial growth factor (VEGF), hypoxia inducible factors 1 α and β, vitamin D activity, and estrogen metabolism as measured by the ratio of 2 hydroxyestrone and 16α-hydroxyestrone. Elucidation of indoor versus outdoor influences on exercise induced metabolism may be important in understanding variations in reports of the protective nature of exercise on breast cancer prevention.

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Do the Effects of Exercise on Breast Cancer Prevention Vary With Environment?

Introduction

During exercise, chemical, neural, and hormonal factors work together to direct blood flow towards the heart and skeletal muscles, and via vasoconstriction, away from areas such as skin, gut, spleen, liver, and kidneys (1). Although no one has documented reduced blood flow to the breasts during moderate exercise, it is likely. The central concept in this proposal is that exercise, by temporarily reducing blood flow to the breasts, induces a transient state of hypoxia. Exercise is known to induce a temporary state of hypoxia (2). Hypoxia increases vascular endothelial growth factor (VEGF) activity in tumor cells (3); hypoxia-inducible factor 1 alpha (HIF-A) (3) and metastatic potential. However, habitual and/or lifetime exercise is a life-style factor associated with a lower incidence of many forms of cancer. The finding that exercise may provide protection against developing many forms of cancer, including breast cancer is paradoxical to the findings about the effects of hypoxia on tumor cells. The mechanisms underlying these phenomena and the apparent paradox have not been identified.

It has also been suggested that sunlight, often a concomitant exposure associated with exercise, can reduce breast cancer risk (4). This raises the question of whether exposure to sunlight during exercise correlates with reduced susceptibility to breast cancer? To answer this question, we will do two experiments. Subjects will exercise for one hour outdoors in the sunlight and one hour indoors on a treadmill in the absence of sunlight.

In an effort to begin to explore this paradox, we reexamined data from a previous study. The preliminary, post hoc analysis revealed that women (with or without breast cancer) who exercised had higher urinary excretion of 2 OHE/16 alpha-OHE1 ratios than women who had breast cancer and/or women that never exercised. These data are consistent with other reports of a lower breast cancer risk associated with higher 2 OHE/16 alpha-OHE1 ratios and suggest that exercise induced changes in estrogen metabolism may be the mechanism providing protection against breast cancer. **Therefore, we hypothesize that exercise-induced hypoxia will decrease susceptibility to or reoccurrence of breast cancer in post-menopausal women.** In order to begin to test that hypothesis, we aim to determine first whether sunlight exposure alters the effects of exercise on vitamin D and estrogen metabolism.

Body of Report

Task 1. Develop Plan for Study Computer Database, Months 1-3

a. **Normal study values will be entered for each outcome variable, so out-of range values will immediately alert investigators to potential problems.**
   Since all analyses are being performed at the end of the study, rather than concurrent with the study, and normal values may not be relevant, we are plotting the values longitudinally for each patient to see where an individual's values might have varied.

b. **Access database will be developed to monitor each volunteer and to record data from laboratory analyses and medical histories.**
   Tracking system is in place.

Task 2. Obtain IRB approval from local institutions (Palmetto Health Alliance and the University of South Carolina).

a. **Done**

Task 3. Obtain IRB approval from the U.S. Army

a. HSRRB **met on October 10, 2001 to review the grant.**
b. HSRRB Board members recommended approving this protocol with modifications October 19, 2001.
c. Modifications are being prepared.

Task 4. Subject Recruitment and Study, Months 5-7

a. **Recruitment of healthy volunteers and selection of eligible subjects is estimated to take 3 months.**
   1. We will rely on word of mouth to recruit healthy postmenopausal women who regularly exercise and take no medications. This may take several months.
   2. Once 10 subjects have been recruited, we will begin the study.

b. **Study will last 2 weeks for each of the 10 subjects.**

Task 5. Data Analysis of Results from Healthy Volunteers, Months 8-12

a. **Meetings with oncologists and member of the Exercise Sciences Department at the University of South Carolina to present preliminary data.**
   1. Meetings will take place as soon as the data are available.

b. **Final meeting with volunteers to explain study results and to answer any questions.**
   1. Meeting is scheduled for September, by which time all the analyses should be completed.

c. **Annual report to USARMC**
   1. This is the annual report to USARMC.

Key Research Accomplishments

1. Narrowed the scope of the research to include only women living at approximately 300 ft (100 meters) in .Columbia, South Carolina.
2. Added Dr. Stephanie Muga as a co-PI.
3. Refined the biological endpoints to be used in the study.
4. Received Scientific Review, local IRB review in South Carolina, and Army HSRRB approvals.

Reportable Outcomes

None yet. Volunteers will be recruited in spring (warm ambient temperatures for outdoor walking) of 2002, and the study will begin at that time.

Conclusions

1. All Human Subjects concerns and Scientific Review concerns have been met.
2. Specific results of the study are not yet available.

References

1. McArdle WD, Katch FI, Katch VL (eds). Exercise Physiology Energy, Nutrition, and Human Performance. Third Edition. (1991) Philadelphia/London: Lea & Febiger. Pg 319-323.

2. Jammes Y, Zattara-Hartmann MC, Badier M. Functional consequences of acute and chronic hypoxia on respiratory and skeletal muscles in mammals. Comparative Biochem & Physiology, Part A. (1997) 118(1):15-22. Sep

3. Ruohola JK, Valve EM, Karkkainen MJ, et al. Vascular endothelial growth factors are differentially regulated by steroid hormones and antiestrogens in breast cancer cells. Molec & Cell Endocrin (1999) 149(1-2):29-40. Mar

4. Zhong H, De Marzo AM, Laughner E, et al. Overexpression of hypoxia-inducible factor 1alpha in common human cancers and their metastases. Cancer Research (1999) 59(22):5830-5. Nov

5. John EM, Schwart GG, Dreon DM, Koo J. Vitamin D and breast cancer risk: the NHANES I epidemiologic follow-up study, 1971-1975 to 1992. Cancer Epi, Biomarkers & Prev (1999) 8:399-406. May

Appendices

None yet.